as a CD163 variant released into the cell culturing media, or a CD163 variant anchored to the cell membrane.

Cultures of cells derived from multicellular organisms represent preferred host cells. In principle, any higher eukaryotic cell culture is workable, whether from vertebrate or invertebrate culture. Examples of useful host cell lines are E-coli, yeast or human cell lines. Preferred host cells are eukaryotic cells known to synthesize endogenous CD163. Cultures of such host cells may be isolated and used as a source of the variant, or used in therapeutic methods of treatment, including therapeutic methods aimed at diagnostic methods carried out on the human or animal body.

Multimers and dimers, including homodimers and heterodimers of variants of CD163 according to the invention, are also provided and fall under the scope of the invention. CD163 functional equivalents and fragments can be produced as homodimers or heterodimers with other amino acid sequences or with native CD163 sequences. Heterodimers include dimers containing a CD163 variant binding at least one Hp-Hb complex when present in a homodimer, and a CD163 fragment that need not have or exert any biologically activity.

The binding affinity of the CD163 variant of the invention and a dimeric Hp-Hb complex preferably has a kD value of between 10-100 nM, such as between 20-80 nM, for example between 40-60 nM, such as between 45-55 nM.

The CD163 variant of the invention preferably has a Kd binding affinity for a multimeric Hp-Hb complex of the invention of between 2-10 nM.

A dimeric Hp-Hb complex preferably has a binding affinity to two CD163 receptors on a cell in the range of from 0.05 to 1.0 nM.

The binding affinity may be determined as discussed in Example 2 and 3 below.

One aspect of the invention relates to a composition comprising at least one purified CD163 receptor and/or at least one purified CD163 receptor variant as defined above.

Another aspect of the invention relates to a composition comprising a Hp-Hb complex or a part thereof or a mimic thereof as defined above.

The composition(s) is(are) particularly useful in the manufacture of a medicament for any of the uses discussed below.

The medicament is preferably suitable for parenteral administration, such as intravenous, intramuscular, subcutaneous, or intravenous administration. Thus, the medicament may further comprise any suitable carriers, adjuvants, and/or additives conventionally used for the preparation of medicaments, in particular medicaments for parenteral administration. Another suitable administration route is via inhalation.

The present invention further relates to the following applications of Hp-Hb complexes and/or a variant thereof. One such use is in the manufacture of a medicament for treatment of conditions related to haemolysis in an individual in need of such treatment. Another such use of at least one CD163 or a variant thereof is for the removal of at least one Hp-Hb complex in serum and/or plasma of an individual. The invention may also be used for the determination of the haemolysis rate of an individual. This may be done by determining the level of the binding activity between the CD163 variant and the Hp-Hb complexes, as an indication of the rate with which red blood cells are lysed.

The invention also relates to the use of at least one CD163 molecule for the identification of at least one Hp-Hb complex in serum and/or plasma of an individual.

In yet another aspect the invention relates to the uses of at least one complex comprising haemoglobin and haptoglobin. For example the complex may be used as a marker for a cell expressing CD163 or a CD163 variant, wherein at least one of the haemoglobin or haptoglobin molecules are labelled. Such cell may be a macrophage. Another use is for the delivery of at least one drug/medicament or at least one gene to a cell expressing CD163 or a CD163 variant. The processes of drug and gene-delivery are mentioned above.

The purpose of drug or gene delivery is to localize the drug to the target site. Such targeted delivery systems often take the form of injectables composed of liposomes and microspheres made of proteins. Polymeric systems share some of the advantages of liposomal systems such as altered pharmacokinetics and biodistribution. While liposomes might have better prospects of biocompatibility and potential for fusion with cells, polymeric microspheres have more controllable release kinetics, better stability in storage, and higher drug-loading levels for some classes of compounds. The delivery system is targetted through a linkage to at least one Hp-Hb complex capable of binding to CD163 or a variant thereof.

The delivery may made in vivo or in vitro, the latter in particular being for experimental purposes.

In particular the drugs and genes delivered may be selected from the medicaments discussed above.

The deliberate introduction of DNA encoding a desired gene, under conditions where the gene may be expressed within the cell and leads to the production of RNA and/or protein, can be desirable in order to provoke any of a wide range of useful biological responses. The Hp-Hb complex can carry heterologous genes under the control of promoters able to cause their expression in vectors.

In another aspect of the invention the gene therapy comprises introducing a nucleic acid sequence to up-regulate or down-regulate expression of a target gene in the host cell, either by means of a protein encoded by the introduced nucleic acid sequence or by means of an anti-sense relation between RNA encoded by the introduced nucleic acid and a target nucleic acid molecule corresponding to an endogenous gene product.

An example of anti-atherosclerotic drugs to be delivered to macrophages by complex formation with Hp-Hb and subsequent uptake via HbSR/CD163:

Specific or non-specific *Peroxisome proliferator-activated receptor (PPAR) agonists* such as polyunsaturated fatty acid (FA), modified Fas, conjugated Fas, oxidized Fas, FA-derived eicosanoids, fibrate normolipidaemic agents (e.g. phenofibrate), antidiabetic gliazones.

One effect of these drugs might be to stimulate PPAR activity and thereby the efflux of cholesterol in macrophage-derived foam cells in atherosclerotic lesions.

In yet another embodiment the substance linked to the Hp-Hb complex or a part thereof or a mimic thereof may also be an antibody directed to a target desired to be cleared from plasma, which is accomplished when the antibody binds the target and the Hp-Hb complex or a part thereof or a mimic thereof linked to the antibody binds a CD163 receptor on for example a macrophage followed by cellular uptake and optional degradation of the target. This embodiment may for example be used for clearing myoglobin from plasma after muscle injuries, using an antibody directed to myoglobin.

In yet another embodiment the Hp-Hb complex mimic linked to a substance may be a fusion protein of an antibody directed to Hp-Hb complex or CD163 receptor and an antibody directed to a target desired to be cleared from the plasma as discussed above.

It is a further object of the present invention that the CD163 or CD163 variant is applied in a method comprising the treatment of haemolysis in an individual in need of such treatment. Lysis of red blood cells may occur in a number of physiological and pathological conditions. The release of haemoglobin to the plasma presents a serious physiological threat. Administration of CD163 or the CD163 variant leads to a binding between the Hp-Hb complexes